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December 3, 1957

Dr. Erwin Chargaff
Cell Chemistry Laboratory
Columbia University
630 West 168th Street
New York 32, N. Y.

Dear Erwin:

Thank you for your note. Just a day ago, the issue of Nature in question arrived in Madison and I had a chance to read your article, which of course interested me very much indeed.

I have nothing more to tell you that would be especially relevant to the technical problems of that work; however, I have a paper in press in the Journal of Bacteriology, which will be coming out very shortly, which gives some more details on the process of reversion and on the relationship between protoplasts and L-form growth of bacteria.

Also included in that text is some mention of our own unsuccessful and otherwise unsuccessful attempts at achieving transduction of genetic markers to protoplast recipients. If your own successful results can be regularized you will, of course, have furnished extremely important tool for genetic research and one that I would be most anxious to be able to exploit at the earliest opportunity. It was, as I am sure you are aware, this possibility which motivated my own diversion to the general problem of the technology of protoplasts in E. coli. You will not be surprised if I approach accomplishments along these lines with a certain sense of hypercriticism perhaps based in part by my own inability to fulfill my initial expectation of the utility of protoplasts for such purposes. The more so as we have conducted experiments identical designs to your own and have run only into red herring along the way.

I wonder if it would be possible for you to allay some of my skepticisms with a more detailed account of the other eleven experiments which were not presented in full in your preliminary note, together with the further information which I am sure you have accumulated. To verify that a chemical agent has indeed induced a genetic change is one of the trickiest problems in bacterial genetics, and very much the more so under the handicap of two of the conditions in your experiments; namely, the very high background of spontaneous reversions already present in your untreated cultures, and the long interval of growth of the treated population, the latter leaving open many possibilities of undetected selective growth. The very nature of spontaneous mutation, its predictable unpredictability, and the exaggeration of this by the clonal distribution

which tends to defy simple statistical analysis confound the problem even more. It would however help me to get a constructive prospective on your experiment if you could give me the figures on the other rungs. I am particularly anxious to know if any of these experiments the treated cultures actually showed a smaller number of reversions than the untreated ones.

If these problems of inference can be dealt with in a system which seems to be inherently irregular in its yielding of positive results, the next urgent question that I would ask is whether the phenomenon conforms to the definition of a genetic transduction (see for example my article in the American Scientist last year). A crucial test for this purpose would be a comparison of the effectiveness of DNA extracted from the wild type and from the same mutant respectively.

May I also inquire whether you have had comparable results with any other mutants as recipient, and indeed whether any others have been tried? I am enclosing a copy of the paper referred to above.

With all best wishes,

Yours sincerely,

Joshua Lederberg
Professor of Medical Genetics

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encl.